

Optical Treatment of Migraines Study Protocol

Version 1.0

February 28, 2019

Sponsor:

Avulux

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Boca Raton, FL 33496

Statement of Compliance

The trial will be conducted in accordance with the Clinical Study Protocol, requirements of the IRB, the Investigator Agreement, and the following Code of Federal Regulations: 21 CFR 812, 21 CFR 50, 21 CFR 54, 21 CFR 56, and 21 CFR 11.

I hereby confirm that I approve of this Clinical Study Protocol and agree to comply with its terms as laid out in this document. I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator:

Print/Type Name:

Signed: _____

Date: _____

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Background and Introduction:

Approximately 9% of men and 18% of women are afflicted with migraines. (Stovner, 2006) Over 90% of patients with migraines report a sensitivity to light (photophobia) during headaches. (Evans, 2008) Some migraine sufferers report that light can trigger a migraine and some have a chronic sensitivity to light. (Main, 1997) Migraineurs are especially sensitive to non-incandescent lighting sources such as fluorescent lights, computer monitors, and gas-vapor lamps.

The pathway that mediates photophobia appears to involve intrinsically photosensitive retinal ganglion cells (IPRGCs, Hattar, 2002) and trigeminal afferents (Nosedá, 2010; Digre and Brennan, 2012). These retinal cells do not require input from photoreceptors to be activated by light, and they have been shown to be responsible for circadian rhythm entrainment and the pupillary light reflex. As such, these cells constitute a pathway separate from that of the visual pathway (Güler, 2008). IPRGCs contain the chromophore melanopsin. Unlike rhodopsin, the photosensitive molecule found in rods and cones, melanopsin is a bi-stable molecule. Although melanopsin is related to rhodopsin, it shares more similarities with the photosensitive molecules found in invertebrate photoreceptors (Mure, 2009). Bi-stable pigments such as melanopsin have two stable isoforms that are spectrally distinct (Figure 1). One isoform is active and can elicit a physiologic response; the other is inactive. Different wavelengths of light (λ_1 and λ_2) trigger a conformational change between the two isoforms. In the case of melanopsin, it is 480 nm light that isomerizes melanopsin from its active to its inactive state and triggers the phototransduction cascade in the IPRGC. In addition to a possible natural slow thermal relaxation back to the cis state, exposure to 590 nm light drives melanopsin from its inactive, all-trans isoform to its active, 11-cis isoform. Although 590 nm light isomerizes melanopsin, it does not activate the cell.

In a previous study, Subhash and Hoggan designed thin-film optical filters for spectacles lenses that blocked light around 480 and 620 nm. Patients with chronic migraines experienced statistically and clinically significant reductions in headache impact as measured by the Headache Impact Test (HIT-6TM) while wearing these filters. However, this study lacked an adequate control intervention.

We hypothesize that if we could selectively block this portion of the visible spectrum, we could reduce the severity of headaches in migraine patients. The objective of this study is to develop optical filters that can be applied to spectacle lenses, contact lenses, and light sources that will block the target wavelengths. The filters will then be tested in a cohort of adult patients with migraines. If successful, these filters could be a novel, non-invasive adjuvant in the treatment of migraines and light sensitivity.

Investigational Device

Avulux™ is intended to decrease the impact of headache and migraine on normal daily life and the ability to function, and reduce the frequency and severity of headache, in adult patients diagnosed with episodic migraine headache or chronic migraine.

Avulux™ consists of a pair of optical filters in the form of spectacle lenses, provided in standard spectacle frames or as clip-on units, coated with a thin film that effectively blocks light at specified wavelength ranges while minimizing distortion of the visible spectrum. The optical filters block a portion of the optical spectrum that is suspected to stimulate photophobic responses that trigger some, and exacerbate most, migraines.

Our active and sham lenses will have tints calibrated such that the optical density, that is the overall “darkness” of all study lenses, will be the same. All study lenses will appear to have the same overall light-blocking effect to study subjects. The optical properties of the two lenses are demonstrated in Figure 1.

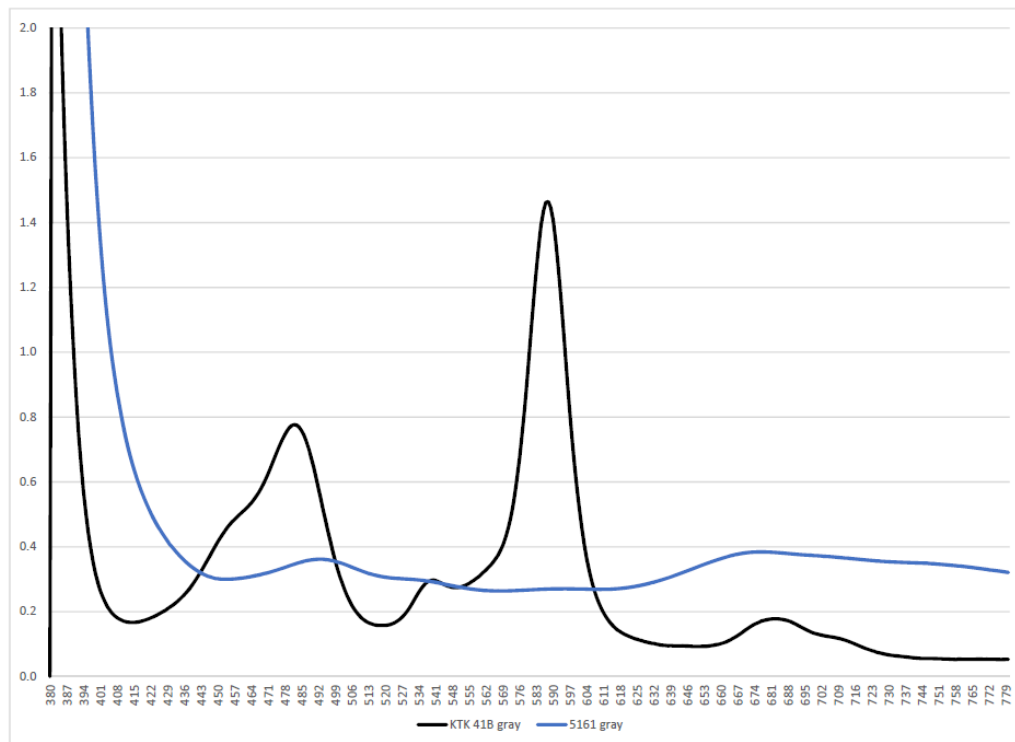


Figure 1. Optical properties of study lenses (black) and sham lenses (blue)

The study spectacles will be fitted with “wear over” frames that can be worn easily by study subjects who wear no corrective lenses, those who wear contacts, or those who normally wear corrective prescription lenses, as noted in the photo below.



Objectives:

The long-term goal of the project is to reduce the impact of headaches in patients with migraine headaches. The goal of this study is to test optical filters that block light at 480 nm and 590 nm. These wavelengths of light are known to activate IPRGCs. IPRGCs are part of the neural mechanism responsible for light-induced pain associated with migraines.

The primary objective of this study is to evaluate the efficacy of the Avulux device in reducing the impact of migraine headaches as measured by improvement in Headache Impact Test (HIT-6™) scores at three weeks when compared to a control/sham device.

Due to the minimal risk of adverse events while using the device, no safety objective is planned for this study, although adverse events (if any) will be recorded and reported.

Anticipated Clinical Benefits

The anticipated benefit of this device is to reduce the impact of headaches in patients with migraine headaches.

Anticipated Risks

There are no anticipated risks from the study or the device, since any potential discomfort experienced from use of the device would be mitigated by removal of the glasses.

Study Design:

This study is a prospective, multi-center, randomized, placebo-controlled, crossover trial. A total of 50 subjects will be randomized into one of two treatment groups in a one-to-one ratio. After three weeks, and following a one-week washout period, subjects will be given spectacles from the other treatment group.

Subjects will be enrolled and followed at a maximum of three clinical sites. It is anticipated each clinical site will enroll 20 to 30 eligible study subjects who have provided written informed consent.

Each principal investigator will be responsible for obtaining Institutional Review Board (IRB) approval prior to conducting this research. All potential subjects will be required to participate in an informed consent process and sign an IRB-approved written informed consent prior to study enrollment.

Patient Recruitment and Screening

Suitable patients may be contacted and pre-screened prior to study commencement, but no study-related procedures are to be undertaken prior to IRB approval, eligibility confirmation, and informed consent.

Enrollment Criteria

The study population will be comprised of up to 50 subjects with a confirmed diagnosis of non-chronic migraines. Subjects will be enrolled at up to three clinical sites. The frequency of migraine headache in females is roughly twice that in males and it is expected that the study population will reflect this gender disparity. Subjects must be geographically accessible throughout the study and be willing and able to attend required follow-up appointments.

Candidates who express interest in study participation will be evaluated for enrollment based upon the following inclusion/exclusion criteria and will be offered informed consent.

Inclusion Criteria:

1. Patient is 18 years or older
2. Patient is willing and able to provide written informed consent
3. Patient is willing and able to complete all scheduled study visits
4. Diagnosis of migraine, based on the following primary headache characteristics (based on the Revised International Headache Society criteria for migraine headache provided in Appendix A):
 - A. At least 5 attacks fulfilling criteria B-D
 - B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
 - C. Headache has at least two of the following characteristics:
 1. unilateral location
 2. pulsating quality
 3. moderate or severe pain intensity
 4. aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)
 - D. During headache at least one of the following:
 1. nausea and/or vomiting
 2. photophobia and phonophobia
 - E. Not attributed to another disorder

Exclusion Criteria:

1. Patients with other light sensitive conditions, such as iritis.
2. Patients who have less than 4 headache days per month
3. Patients who have chronic daily headaches.
4. Patients who have had any change in their migraine treatment within the 4 weeks prior to the trial onset.

For the purposes of this study, patients will be considered enrolled (study subjects) following informed consent.

Study Procedures

Visit 1:

At the enrollment visit, each subject will complete an initial/baseline HIT-6 inventory. They will then be randomized to receive spectacles having either the optical filter or a conventional tint. A randomized permuted block randomization will be employed.

All spectacles will have the same overall optical density across the visible spectrum. This statement means that all study eyewear will appear to have the same amount of “darkness” to the subject. Subjects will be instructed to use the spectacles for three weeks. They will be instructed to put the spectacles on at the first signs or symptoms of their migraine attacks. This could be their usual aura, or the first signs of their headache commencing, and to keep the spectacles on until their headache has resolved.

The study spectacles will be fitted with “wear over” frames that can be worn easily by study subjects who wear no corrective lenses, those that wear contacts, or those that normally wear corrective prescription lenses.

Visit 2 (3 weeks \pm 2 days):

After three weeks they will return to the study site to complete the HIT-6 inventory and turn in their glasses. They will then undergo a washout period for 7 days. During the washout period subjects will have no access to study glasses, but will be expected to take their current migraine medications as needed/prescribed.

Visit 3 (4 weeks \pm 2 days):

After the washout period, subjects will return to the study site to receive new spectacles from the opposite treatment group, complete another HIT-6 inventory and then repeat the three week treatment period with the other lenses.

Visit 4 (7 weeks \pm 3 days):

After the second treatment period, the subjects will return to the study site to turn in their spectacles and complete the final HIT-6 inventory.

Patient Reported Outcome Data

Subjects will be asked to complete the 6-item Headache Impact Test (HIT-6TM) inventory at baseline, week 3, week 4 and week 7. A copy of the HIT-6TM is attached. Subjects will also be asking to keep daily diaries throughout the 8-week study detailing the frequency and severity of their headaches, a numerical pain score of their headaches, and their need for abortive medications in addition to the use of the spectacles.

Study coordinators will contact subjects once per week to insure they are completing their diaries and wearing their study-related spectacles. These weekly contacts will also enable coordinators to identify and address any barriers to adherence with the protocol. These contacts will help maximize retention and minimize loss to follow-up.

Patient Withdrawal or Termination

Study participants can choose to withdraw from participation in the study at any time during the process for any reason upon request. Additionally, subjects may be removed from the study at any point if the Investigator determines that the patient should be discontinued.

Standard of Care vs. Research-Related Procedures:

All procedures are research-related.

Study Oversight

Safety Committees

This protocol does not pose any significant risk to subjects. Third-party safety committees (i.e., clinical events committees or data safety and monitoring boards) are not included.

Study Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with federal regulations, agreements with the sponsor, the currently approved protocol, and with any requirements imposed by the IRB.

1. Site monitoring will be performed by a third party CRO working on behalf of Avulux, Inc.
2. Monitors will be qualified by training and experience to monitor the study.
3. A Clinical Monitoring Plan (CMP) will be developed to establish the plan for study oversight.
4. On-site monitoring is anticipated throughout the course of the study.
5. The sponsor will be provided with written reports of these visits, and the sites will be provided with a follow-up letter describing the findings and defining any outstanding issues or action items required

Statistical Methods, Data Analysis and Interpretation

Preliminary Analyses

Baseline characteristics will be summarized by randomized treatment group with standardized differences between treatment groups used to assess the balance of patient characteristics between the two groups. Univariate summaries will also be performed at baseline and follow-up for the primary and secondary outcome variables. If quantitative outcome variables exhibit substantial skewness, transformations may be sought to better approximate normality.

Primary Outcome

The primary outcome measure is the HIT-6 Total Score. Additionally, we will focus on the first two questions of the HIT-6 which relate specifically to the severity of the migraine and its effect on activities of daily living.

Required Sample Size

In a preceding crossover trial, the pooled cross-sectional SD for the follow-up HIT values across the two periods was 7.60. Assuming a SD in the HIT-6 score of 7.6 points, and allowing for 10% loss-to-follow-up, 50 randomized crossover subjects will provide 80% power with 2-sided $\alpha=0.05$ to detect a mean difference in HIT score of 3.5 points. The effect size of 3.5 points is just under half the SD of 7.6 points assumed in our power calculations, and thus represents a moderate effect size.

Secondary Outcome

To measure effects on the number and severity of headaches, we will use the subjects' daily diaries to count the number of days with headache that either a) made activity difficult, b) caused activity changes, or c) caused patient to go to bed. We will then compare the proportion of days with headaches that met one of these criteria for the 4-week baseline period and the 3-week intervention.

Exploratory Outcomes

1. Proportion of subjects who were able to move out of the "very severe impact" category of the HIT-6 during the 3-week intervention.
2. Proportion of patients who experienced at least a 5-point improvement in their HIT-6 score during the 3-week intervention.
3. Proportion of days with headaches which lead to use of medications to control the headache over the 3-week intervention.
4. Proportion of days with light sensitivity over the 3-week intervention.
5. Average Number of Hours Slept over the 3-week intervention.

Analysis Plan for Secondary and Exploratory Outcomes

Based on the initial descriptive summaries, each of the above secondary outcomes will be classified into one of the following categories:

- a) Numeric outcomes which are approximately normally distributed.
- b) Numeric outcomes which can be transformed to approximate normal distributions.
- c) Numeric outcomes which deviate substantially from normality and will be analyzed non-parametrically.
- d) Numeric outcomes with substantial floor or ceiling effects that will be analyzed as dichotomous outcomes.

Numeric outcomes that can be transformed to approximate normality. All the secondary and exploratory outcomes assigned to categories (a) or (b) will be analyzed using analyses of covariance (ANCOVAs) to compare the outcomes between the treatment and control groups after controlling for the corresponding outcomes during the baseline phase of the study.

Nonparametric Analyses. Secondary outcomes assigned to category (c) will be analyzed by comparing the changes from baseline to the 4-week follow-up assessment between the treatment groups using Wilcoxon rank sums tests.

Binary Outcomes. Outcomes assigned to category (d) will be analyzed by applying exact Mantel-Haenszel tests to compare the 4-week follow-up values between the treatment groups, with stratification for the baseline level of each outcome. Baseline levels will be stratified by tertiles.

Multiple comparisons. Multiple comparisons. The secondary outcome will be compared between the randomized groups using a 2-sided α level of 0.05, without adjustment for multiple comparisons. The exploratory outcomes will also be compared between the treatment groups using a 2-sided α level of 0.05, without adjustment for multiple comparisons. However, interpretation of results for the exploratory outcomes will take into account the risk of Type 1 errors resulting from multiple hypothesis tests.

Missing Data. The analysis of the primary outcome as well as other outcomes using linear mixed effects models will be approximately unbiased so long as the pattern of missing data is missing at random, meaning that the probability that an outcome measurement is missing may depend on the values of other non-missing measurements, but not on the value of the missing measurement itself. Should the fraction of missing measurements for the primary outcome exceed 10%, sensitivity analyses will be performed in which multiple imputation is used to impute missing data.

Control of Investigational Devices/Drugs:

Avulux, Inc. will maintain ownership of all devices provided to sites for testing. Clinical sites are expected to ensure the device is stored securely, yet available to study staff authorized to dispense the devices to study subjects. At the end of the study, sites will be asked to return any and all received devices back to Avulux.

All study lenses will be numbered and stored in a locked cabinet. Only authorized study staff will have access to spectacles. Devices will be tracked on provided inventory logs.

Abbreviated Device Regulations for Nonsignificant Risk (NSR) Devices:

Nonsignificant risk determination

21 CFR 812.3 contains the following definition of “Significant risk device”:

(m) *Significant risk device* means an investigational device that:

- (1) Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
- (2) Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
- (3) Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- (4) Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

The FDA guidance document concerning significant and nonsignificant risk assessments (*"Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors Significant Risk and Nonsignificant Risk Medical Device Studies"*; US Department of Health and Human Services, Food and Drug Administration; January 2006.) contains the following information:

A. What is a Significant Risk Device Study?

Under 21 CFR 812.3(m), an SR device means an investigational device that:

Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;

Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;

Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or

Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

B. What is a Nonsignificant Risk Device Study?

An NSR device study is one that does not meet the definition for an SR device study.

C. Who Decides Whether A Device Study is SR or NSR?

Sponsors are responsible for making the initial risk determination and presenting it to the IRB.

FDA is also available to help the sponsor, clinical investigator, and IRB in making the risk determination.

X. EXAMPLES OF NSR AND SR DEVICES

The following examples may help sponsors and IRBs in making SR and NSR determinations. The list includes many commonly studied medical devices. Inclusion of a device in the NSR list is not a final determination because the evaluation of risk must reflect the proposed use of a device in a study.

A. Nonsignificant Risk Devices

- Caries Removal Solution
- Contact Lens Solutions intended for use directly in the eye (e.g., lubricating/rewetting solutions) using active ingredients or preservation systems with a history of prior ophthalmic/contact lens use or generally recognized as safe for ophthalmic use

- Conventional Gastroenterology and Urology Endoscopes and/or Accessories
- Conventional General Hospital Catheters (long-term percutaneous, implanted, subcutaneous and intravascular)
- Conventional Implantable Vascular Access Devices (Ports)
- Conventional Laparoscopes, Culdoscopes, and Hysteroscopes
- Daily Wear Contact Lenses and Associated Lens Care Products not intended for use directly in the eye (e.g., cleaners; disinfecting, rinsing and storage solutions)
- Dental Filling Materials, Cushions or Pads made from traditional materials and designs
- Denture Repair Kits and Realignment
- Digital Mammography
- Electroencephalography (e.g., new recording and analysis methods, enhanced diagnostic capabilities, measuring depth of anesthesia if anesthetic administration is not based on device output)
- Externally Worn Monitors for Insulin Reactions
- Functional Non-Invasive Electrical Neuromuscular Stimulators
- General Biliary Catheters
- General Urological Catheters (e.g., Foley and diagnostic catheters) for short term use (< 28 days)
- Jaundice Monitors for Infants
- Low Power Lasers for treatment of pain
- Magnetic Resonance Imaging (MRI) Devices within FDA specified parameters
- Manual Image Guided Surgery
- Menstrual Pads (Cotton or Rayon, only)
- Menstrual Tampons (Cotton or Rayon, only)
- Nonimplantable Electrical Incontinence Devices
- Nonimplantable Male Reproductive Aids with no components that enter the vagina
- Ob/Gyn Diagnostic Ultrasound within FDA approved parameters
- Partial Ossicular Replacement Prosthesis (PORP)
- Total Ossicular Replacement Prosthesis (TORP)
- Transcutaneous Electric Nerve Stimulation (TENS) Devices for treatment of pain (except for chest pain/angina)
- Ureteral Stents
- Urethral Occlusion Device for less than 14 days
- Wound Dressings, excluding absorbable hemostatic devices and dressings (also excluding Interactive Wound and Burn Dressings that aid or are intended to aid in the healing process)

The Avulux study will follow abbreviated requirements from 21 CFR 812.2:

(b) *Abbreviated requirements.* The following categories of investigations are considered to have approved applications for IDE's, unless FDA has notified a sponsor under 812.20(a) that approval of an application is required:

- (1) An investigation of a device other than a significant risk device, if the device is not a banned device and the sponsor:
 - (i) Labels the device in accordance with 812.5;
 - (ii) Obtains IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintains such approval;
 - (iii) Ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, informed consent under part 50 and documents it, unless documentation is waived by an IRB under 56.109(c).
 - (iv) Complies with the requirements of 812.46 with respect to monitoring investigations;
 - (v) Maintains the records required under 812.140(b) (4) and (5) and makes the reports required under 812.150(b) (1) through (3) and (5) through (10);
 - (vi) Ensures that participating investigators maintain the records required by 812.140(a)(3)(i) and make the reports required under 812.150(a) (1), (2), (5), and (7); and
 - (vii) Complies with the prohibitions in 812.7 against promotion and other practices.

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APPENDIX A: Revised International Headache Society criteria for migraine headache

(Source: http://ihs-classification.org/en/02_klassifikation/05_anhang/01.05.01_anhang.html).

1.1 Migraine without aura

Description:

Recurrent headache disorder manifesting in attacks lasting 4-72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia

Diagnostic criteria:

- F. At least 5 attacks¹ fulfilling criteria B-D
- G. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)^{2;3;4}
- H. Headache has at least two of the following characteristics:
 - 5. unilateral location^{5;6}
 - 6. pulsating quality⁷
 - 7. moderate or severe pain intensity
 - 8. aggravation by or causing avoidance of routine physical activity (**eg**, walking or climbing stairs)
- I. During headache at least one of the following:
 - 1. nausea and/or vomiting
 - 2. photophobia and phonophobia⁸
- J. Not attributed to another disorder⁹

Notes:

- 1. Differentiating between 1.1 **Migraine without aura** and 2.1 **Infrequent episodic tension-type headache** may be difficult. Therefore at least 5 attacks are required. Individuals who otherwise meet criteria for 1.1 **Migraine without aura** but have had fewer than 5 attacks should be coded 1.6.1 **Probable migraine without aura**.
- 2. When the patient falls asleep during migraine and wakes up without it, duration of the attack is reckoned until the time of awakening.
- 3. In children, attacks may last 1-72 hours (although the evidence for untreated durations of less than 2 hours in children requires corroboration by prospective diary studies).
- 4. When attacks occur on ≥15 days/month for >3 months, code as 1.1 **Migraine without aura** and as 1.5.1 **Chronic migraine**.
- 5. Migraine headache is commonly bilateral in young children; an adult pattern of unilateral pain usually emerges in late adolescence or early adult life.

6. Migraine headache is usually frontotemporal. Occipital headache in **children**, whether unilateral or bilateral, is rare and calls for diagnostic caution; many cases are attributable to structural lesions.
7. **Pulsating** means throbbing or varying with the heartbeat.
8. In young children, photophobia and phonophobia may be inferred from their behaviour.
9. 9. History and physical and neurological examinations do not suggest any of the disorders listed in groups 5-12, or history and/or physical and/or neurological examinations do suggest such disorder but it is ruled out by appropriate investigations, or such disorder is present but attacks do not occur for the first time in close temporal relation to the disorder.

1.2 Migraine with aura

Description:

Recurrent disorder manifesting in attacks of reversible focal neurological symptoms that usually develop gradually over 5-20 minutes and last for less than 60 minutes. Headache with the features of migraine without aura usually follows the aura symptoms. Less commonly, headache lacks migrainous features or is completely absent.

Diagnostic criteria:

- A. At least 2 attacks fulfilling criterion B
- B. Migraine aura fulfilling criteria B and C for one of the subforms 1.2.1-1.2.6
- C. Not attributed to another disorder¹

Note:

1. History and physical and neurological examinations do not suggest any of the disorders listed in groups 5-12, or history and/or physical and/or neurological examinations do suggest such disorder but it is ruled out by appropriate investigations, or such disorder is present but attacks do not occur for the first time in close temporal relation to the disorder.

Comments:

The aura is the complex of neurological symptoms that occurs just before or at the onset of migraine headache. Most patients with migraine have exclusively attacks without aura. Many patients who have frequent attacks with aura also have attacks without aura (code as 1.2 **Migraine with aura** and 1.1 **Migraine without aura**).

Premonitory symptoms occur hours to a day or two before a migraine attack (with or without aura). They include various combinations of fatigue, difficulty in concentrating, neck stiffness, sensitivity to light or sound, nausea, blurred vision, yawning and pallor. The terms **prodrome and warning symptoms** are best avoided because they are often mistakenly used to include aura.

The majority of migraine auras are associated with headache fulfilling criteria for 1.1 **Migraine without aura**. For this reason the entity 1.2.1 **Typical aura with migraine headache** has been singled out below. Migraine aura is sometimes associated with a headache that does not fulfil criteria for migraine without aura and, in other cases, migraine aura may occur without headache. These two subforms are also now distinguished.

Aura with similar features has also been described in association with other well-defined headache types, including cluster headache; the relationships between aura and headache are not fully understood.

Before or simultaneously with the onset of aura symptoms, regional cerebral blood flow is decreased in cortex corresponding to the clinically affected area and often including an even wider area. Blood flow reduction usually starts posteriorly and spreads anteriorly and is usually above the ischaemic threshold. After one to several hours, gradual transition into hyperaemia occurs in the same region. Cortical spreading depression of Leão has been implicated.

Systematic studies have demonstrated that many patients with visual auras occasionally have symptoms in the extremities. Conversely patients with symptoms in the extremities virtually always also suffer visual aura symptoms. A distinction between migraine with visual aura and hemiparaesthetic migraine is probably artificial and therefore is not recognised in this classification. Patients with motor weakness are classified separately because of the dominantly inherited form, **1.2.4 Familial hemiplegic migraine**, and because of clinical differences. The genetic relationship between migraine with aura and familial hemiplegic migraine has not been established.

The previously-defined syndromes **migraine with prolonged aura** and **migraine with acute-onset aura** have been abandoned. The great majority of patients with such attacks have other attacks that fulfil criteria for one of the subforms of **1.2 Migraine with aura** and should be coded to that diagnosis. The rest should be coded to **1.6.2 Probable migraine with aura** specifying the atypical feature (prolonged aura or acute-onset aura) in parenthesis.

1.2.1 Typical aura with migraine headache

Description:

Recurrent disorder manifesting in attacks of reversible focal neurological symptoms that usually develop gradually over 5-20 minutes and last for less than 60 minutes. Headache with the features of migraine without aura usually follows the aura symptoms. Less commonly, headache lacks migrainous features or is completely absent.

Diagnostic criteria:

- A. At least 2 attacks fulfilling criterion B
- B. Migraine aura fulfilling criteria B and C for one of the subforms 1.2.1-1.2.6
- C. Not attributed to another disorder¹

Note:

History and physical and neurological examinations do not suggest any of the disorders listed in groups 5-12, or history and/or physical and/or neurological examinations do suggest such disorder but it is ruled out by appropriate investigations, or such disorder is present but attacks do not occur for the first time in close temporal relation to the disorder.

Comments:

The aura is the complex of neurological symptoms that occurs just before or at the onset of migraine headache. Most patients with migraine have exclusively attacks without aura. Many patients who have frequent attacks with aura also have attacks without aura (code as **1.2 Migraine with aura** and **1.1 Migraine without aura**).

Premonitory symptoms occur hours to a day or two before a migraine attack (with or without aura). They include various combinations of fatigue, difficulty in concentrating, neck stiffness, sensitivity to light or sound, nausea, blurred vision, yawning and pallor. The terms **prodrome**

and warning symptoms are best avoided because they are often mistakenly used to include aura.

The majority of migraine auras are associated with headache fulfilling criteria for 1.1 **Migraine without aura**. For this reason the entity 1.2.1 **Typical aura with migraine headache** has been singled out below. Migraine aura is sometimes associated with a headache that does not fulfil criteria for migraine without aura and, in other cases, migraine aura may occur without headache. These two subforms are also now distinguished.

Aura with similar features has also been described in association with other well-defined headache types, including cluster headache; the relationships between aura and headache are not fully understood.

Before or simultaneously with the onset of aura symptoms, regional cerebral blood flow is decreased in cortex corresponding to the clinically affected area and often including an even wider area. Blood flow reduction usually starts posteriorly and spreads anteriorly and is usually above the ischaemic threshold. After one to several hours, gradual transition into hyperaemia occurs in the same region. Cortical spreading depression of Leão has been implicated.

Systematic studies have demonstrated that many patients with visual auras occasionally have symptoms in the extremities. Conversely patients with symptoms in the extremities virtually always also suffer visual aura symptoms. A distinction between migraine with visual aura and hemiparaesthetic migraine is probably artificial and therefore is not recognised in this classification. Patients with motor weakness are classified separately because of the dominantly inherited form, 1.2.4 **Familial hemiplegic migraine**, and because of clinical differences. The genetic relationship between migraine with aura and familial hemiplegic migraine has not been established.

The previously-defined syndromes **migraine with prolonged aura** and **migraine with acute-onset aura** have been abandoned. The great majority of patients with such attacks have other attacks that fulfil criteria for one of the subforms of 1.2 **Migraine with aura** and should be coded to that diagnosis. The rest should be coded to 1.6.2 **Probable migraine with aura** specifying the atypical feature (prolonged aura or acute-onset aura) in parenthesis.

1.2.2 **Typical aura with non-migraine headache**

Description:

Typical aura consisting of visual and/or sensory and/or speech symptoms. Gradual development, duration no longer than one hour, a mix of positive and negative features and complete reversibility characterise the aura which is associated with a headache that does not fulfil criteria for 1.1 **Migraine without aura**.

Diagnostic criteria:

- A. At least 2 attacks fulfilling criteria B-D
- B. Aura consisting of at least one of the following, but no motor weakness:

1. fully reversible visual symptoms including positive features (eg, flickering lights, spots or lines) and/or negative features (ie, loss of vision)
 2. fully reversible sensory symptoms including positive features (ie, pins and needles) and/or negative features (ie, numbness)
 3. fully reversible dysphasic speech disturbance
- C. At least two of the following:
1. homonymous visual symptoms¹ and/or unilateral sensory symptoms
 2. at least one aura symptom develops gradually over ≥ 5 minutes and/or different aura symptoms occur in succession over ≥ 5 minutes
 3. each symptom lasts ≥ 5 and ≤ 60 minutes
- D. Headache that does not fulfil criteria B-D for 1.1 **Migraine without aura** begins during the aura or follows aura within 60 minutes
- E. Not attributed to another disorder²

Notes:

1. Additional loss or blurring of central vision may occur.
2. History and physical and neurological examinations do not suggest any of the disorders listed in groups 5-12, or history and/or physical and/or neurological examinations do suggest such disorder but it is ruled out by appropriate investigations, or such disorder is present but attacks do not occur for the first time in close temporal relation to the disorder.

Comment:

In the absence of headache fulfilling criteria for 1.1 **Migraine without aura**, precise diagnosis of aura and its distinction from mimics that may signal serious disease (eg, transient ischaemic attack) become much more important.

1.2.3 Typical aura without headache

Description:

Typical aura consisting of visual and/or sensory symptoms with or without speech symptoms. Gradual development, duration no longer than one hour, a mix of positive and negative features and complete reversibility characterise the aura which is not associated with headache.

Diagnostic criteria:

- A. At least 2 attacks fulfilling criteria B-D
- B. Aura consisting of at least one of the following, with or without speech disturbance but no motor weakness:

1. fully reversible visual symptoms including positive features (eg, flickering lights, spots or lines) and/or negative features (ie, loss of vision)
 2. fully reversible sensory symptoms including positive features (ie, pins and needles) and/or negative features (ie, numbness)
- C. At least two of the following:
1. homonymous visual symptoms¹ and/or unilateral sensory symptoms
 2. at least one aura symptom develops gradually over ≥ 5 minutes and/or different aura symptoms occur in succession over ≥ 5 minutes
 3. each symptom lasts ≥ 5 and ≤ 60 minutes
- D. Headache does not occur during aura nor follow aura within 60 minutes
- E. Not attributed to another disorder²

Notes:

1. Additional loss or blurring of central vision may occur.
2. History and physical and neurological examinations do not suggest any of the disorders listed in groups 5-12, or history and/or physical and/or neurological examinations do suggest such disorder but it is ruled out by appropriate investigations, or such disorder is present but attacks do not occur for the first time in close temporal relation to the disorder.

Comments:

In some patients a typical aura is always followed by migraine headache, but many patients have, in addition, attacks with aura followed by non-migraine headache or even without headache. A small number of patients have 1.2.3 **Typical aura without headache** exclusively. More commonly, as patients with 1.2.1 **Typical aura with migraine headache** become older, their headache may lose migraine characteristics or disappear completely even though auras continue. Some individuals, primarily males, have 1.2.3 **Typical aura without headache** from onset.

In the absence of headache fulfilling criteria for 1.1 **Migraine without aura**, precise diagnosis of aura and its distinction from mimics that may signal serious disease (eg, transient ischaemic attack) become much more important. This distinction may require investigation. Especially if aura begins after age 40, if negative features (eg, hemianopia) are predominant, or if aura is prolonged or very short, other causes should be ruled out.

1.2.4 Familial hemiplegic migraine (FHM)

Description:

Migraine with aura including motor weakness and at least one first- or second-degree relative has migraine aura including motor weakness.

Diagnostic criteria:

- A. At least 2 attacks fulfilling criteria B and C
- B. Aura consisting of fully reversible motor weakness and at least one of the following:
 - 1. fully reversible visual symptoms including positive features (**eg**, flickering lights, spots or lines) and/or negative features (**ie**, loss of vision)
 - 2. fully reversible sensory symptoms including positive features (**ie**, pins and needles) and/or negative features (**ie**, numbness)
 - 3. fully reversible dysphasic speech disturbance
- C. At least two of the following:
 - 1. at least one aura symptom develops gradually over ≥ 5 minutes and/or different aura symptoms occur in succession over ≥ 5 minutes
 - 2. each aura symptom lasts ≥ 5 minutes and < 24 hours
 - 3. headache fulfilling criteria B-D for 1.1 **Migraine without aura** begins during the aura or follows onset of aura within 60 minutes
- D. At least one first- or second-degree relative has had attacks fulfilling these criteria A-E
- E. Not attributed to another disorder¹

Note:

- 1. History and physical and neurological examinations do not suggest any of the disorders listed in groups 5-12, or history and/or physical and/or neurological examinations do suggest such disorder but it is ruled out by appropriate investigations, or such disorder is present but attacks do not occur for the first time in close temporal relation to the disorder.

Comments:

It may be difficult to distinguish weakness from sensory loss.

New genetic data have allowed a more precise definition of FHM than previously. Specific genetic subtypes of 1.2.4 **Familial hemiplegic migraine** have been identified: in FHM1 there are mutations in the CACNA1A gene on chromosome 19, and in FHM2 mutations occur in the ATP1A2 gene on chromosome 1. If genetic testing is done, the genetic subtype should be specified parenthetically.

It has been shown that FHM1 very often has basilar-type symptoms in addition to the typical aura symptoms and that headache is virtually always present. During FHM1 attacks, disturbances of consciousness (sometimes including coma), fever, CSF pleocytosis and confusion can occur. FHM1 attacks can be triggered by (mild) head trauma. In approximately 50% of FHM1 families, chronic progressive cerebellar ataxia occurs independently of the migraine attacks.

FHM is very often mistaken for epilepsy, and (unsuccessfully) treated as such.

1.2.5 Sporadic hemiplegic migraine

Description:

Migraine with aura including motor weakness but no first- or second-degree relative has aura including motor weakness.

Diagnostic criteria:

- A. At least 2 attacks fulfilling criteria B and C
- B. Aura consisting of fully reversible motor weakness and at least one of the following:
 - 1. fully reversible visual symptoms including positive features (eg, flickering lights, spots or lines) and/or negative features (**ie**, loss of vision)
 - 2. fully reversible sensory symptoms including positive features (**ie**, pins and needles) and/or negative features (**ie**, numbness)
 - 3. fully reversible dysphasic speech disturbance
- C. At least two of the following:
 - 1. at least one aura symptom develops gradually over ≥ 5 minutes and/or different aura symptoms occur in succession over ≥ 5 minutes
 - 2. each aura symptom lasts ≥ 5 minutes and < 24 hours
 - 3. headache fulfilling criteria B-D for 1.1 **Migraine without aura** begins during the aura or follows onset of aura within 60 minutes
- D. No first- or second-degree relative has attacks fulfilling these criteria A-E
- E. Not attributed to another disorder¹

Note:

- 1. History and physical and neurological examinations do not suggest any of the disorders listed in groups 5-12, or history and/or physical and/or neurological examinations do suggest such disorder but it is ruled out by appropriate investigations, or such disorder is present but attacks do not occur for the first time in close temporal relation to the disorder.

Comments:

Epidemiological studies have shown that sporadic cases occur with approximately the same prevalence as familial cases. The attacks have the same clinical characteristics as those in 1.2.4 **Familial hemiplegic migraine**.

Sporadic cases always require neuroimaging and other tests to rule out other cause. A lumbar puncture is also necessary to rule out pseudomigraine with temporary neurological symptoms and lymphocytic pleocytosis. This condition is more prevalent in males and often associated with transient hemiparesis and aphasia.

1.2.6 Basilar-type migraine

Description:

Migraine with aura symptoms clearly originating from the brainstem and/or from both hemispheres simultaneously affected, but no motor weakness.

Diagnostic criteria:

- A. At least 2 attacks fulfilling criteria B-D
- B. Aura consisting of at least two of the following fully reversible symptoms, but no motor weakness:
 - 1. dysarthria
 - 2. vertigo
 - 3. tinnitus
 - 4. hypacusia
 - 5. diplopia
 - 6. visual symptoms simultaneously in both temporal and nasal fields of both eyes
 - 7. ataxia
 - 8. decreased level of consciousness
 - 9. simultaneously bilateral paraesthesias
- C. At least one of the following:
 - 1. at least one aura symptom develops gradually over ≥ 5 minutes and/or different aura symptoms occur in succession over ≥ 5 minutes
 - 2. each aura symptom lasts ≥ 5 and ≤ 60 minutes
- D. Headache fulfilling criteria B-D for 1.1 **Migraine without aura** begins during the aura or follows aura within 60 minutes
- E. Not attributed to another disorder¹

Note:

1. History and physical and neurological examinations do not suggest any of the disorders listed in groups 5-12, or history and/or physical and/or neurological examinations do suggest such disorder but it is ruled out by appropriate investigations, or such disorder is present but attacks do not occur for the first time in close temporal relation to the disorder.

Comments:

Basilar-type attacks are mostly seen in young adults. Many patients who have basilar-type attacks also report attacks with typical aura (code for both disorders).

If motor weakness is present, code as 1.2.4 **Familial hemiplegic migraine** or 1.2.5 **Sporadic hemiplegic migraine**. Patients with 1.2.4 **Familial hemiplegic migraine** have basilar-type symptoms in 60% of cases. Therefore, 1.2.6 **Basilar-type migraine** should be diagnosed only when no motor weakness occurs.

Many of the symptoms listed under criterion B are subject to misinterpretation as they may occur with anxiety and hyperventilation.

Originally the terms **basilar artery migraine** or **basilar migraine** were used but, since involvement of the basilar artery territory is uncertain (ie, the disturbance may be bihemispheric), the term **basilar-type migraine** is preferred.

APPENDIX B: HEADACHE IMPACT TEST (HIT-6)

HIT-6™ (VERSION 1.1)

This questionnaire was designed to help you describe and communicate the way you feel and what you cannot do because of headaches.

To complete, please circle one answer for each question.



1 When you have headaches, how often is the pain severe?

Never Rarely Sometimes Very Often Always

2 How often do headaches limit your ability to do usual daily activities including household work, work, school, or social activities?

Never Rarely Sometimes Very Often Always

3 When you have a headache, how often do you wish you could lie down?

Never Rarely Sometimes Very Often Always

4 In the past 4 weeks, how often have you felt too tired to do work or daily activities because of your headaches?

Never Rarely Sometimes Very Often Always

5 In the past 4 weeks, how often have you felt fed up or irritated because of your headaches?

Never Rarely Sometimes Very Often Always

6 In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities?

Never Rarely Sometimes Very Often Always

▼ + ▼ + ▼ + ▼ + ▼
COLUMN 1 (6 points each) COLUMN 2 (8 points each) COLUMN 3 (10 points each) COLUMN 4 (11 points each) COLUMN 5 (13 points each)

To score, add points for answers in each column.

Please share your HIT-6 results with your doctor.

Total Score

Higher scores indicate greater impact on your life.

Score range is 36-78.

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HEADACHE IMPACT TEST™

What Does Your Score Mean?

▼ If You Scored 60 or More

Your headaches are having a very severe impact on your life. You may be experiencing disabling pain and other symptoms that are more severe than those of other headache sufferers. Don't let your headaches stop you from enjoying the important things in your life, like family, work, school or social activities.

Make an appointment **today** to discuss your HIT-6 results and your headaches with your doctor.

▼ If You Scored 56 – 59

Your headaches are having a substantial impact on your life. As a result you may be experiencing severe pain and other symptoms, causing you to miss some time from family, work, school, or social activities.

Make an appointment **today** to discuss your HIT-6 results and your headaches with your doctor.

▼ If You Scored 50 – 55

Your headaches seem to be having some impact on your life. Your headaches should not make you miss time from family, work, school, or social activities.

Make sure you discuss your HIT-6 results and your headaches at your next appointment with your doctor.

▼ If You Scored 49 or Less

Your headaches seem to be having little to no impact on your life at this time. We encourage you to take HIT-6 monthly to continue to track how your headaches affect your life.

▼ If Your Score on HIT-6 is 50 or Higher

You should share the results with your doctor. Headaches that are disrupting your life could be migraine.

Take HIT-6 with you when you visit your doctor because research shows that when doctors understand exactly how badly headaches affect the lives of their patients, they are much more likely to provide a successful treatment program, which may include medication.

HIT is also available on the Internet at www.headachetest.com.

The Internet version allows you to print out a personal report of your results as well as a special detailed version for your doctor.

Don't forget to take HIT-6 again or try the Internet version to continue to monitor your progress.

▼ About HIT

The Headache Impact Test (HIT) is a tool used to measure the impact headaches have on your ability to function on the job, at school, at home and in social situations. Your score shows you the effect that headaches have on normal daily life and your ability to function. HIT was developed by an international team of headache experts from neurology and primary care medicine in collaboration with the psychometricians who developed the SF-36® health assessment tool.

HIT is not intended to offer medical advice regarding medical diagnosis or treatment. You should talk to your healthcare provider for advice specific to your situation.

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HIT-6 Scoring Interpretation English Version 1.1
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